REMARKS

Claims 155, 161, 167, 173-177, 183-186, 192-195 and 201-204 presently appear in the case. No claims have been allowed. The official action of July 29, 2005, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a therapeutic composition that comprises a pharmaceutical formulation of a pharmaceutically acceptable carrier and a human or genetically-engineered monoclonal antibody or antibody binding fragment thereof. The antibody is one that either recognizes an epitope within residues 1-28 of human β-amyloid or is obtainable using residues 1-28 of β-amyloid as an immunogen. Furthermore, the antibody either inhibits aggregation of human β-amyloid or maintains the solubility of soluble human β-amyloid.

MPEP §1453.V.D. states with respect to the amendment of new claims:

> Although the presentation of the amended claim does not contain any indication of what is changed from the previous version of the claim, applicant must point out what is changed in the "Remarks" portion of the amendment.

All of claims 155, 161, 167, 173-177, 183-186, 192-195, 201-204 are previously presented new claims in the sense that they were not present in the patent as issued and are being amended by the present amendment. So that the examiner can see how the claims are being amended from the previous version of

these claims, the following is a recitation of all of these claims shown in the conventional amended format:

155 (Amended). The ~~pharmaceutical formulation~~therapeutic composition of any one of claims ~~150-154~~174-177, wherein said beta-amyloid is human beta-amyloid.

161 (Amended). The ~~pharmaceutical composition~~therapeutic composition of any one of claims ~~156-160~~183-186, wherein said beta-amyloid is human beta-amyloid.

167 (Amended). The ~~pharmaceutical composition~~therapeutic composition of any one of claims ~~162-166~~192-195, wherein said beta-amyloid is human beta-amyloid.

173 (Amended). The ~~pharmaceutical composition~~therapeutic composition of any one of claims ~~168-172~~201-204, wherein said beta-amyloid is human beta-amyloid.

174 (Amended). A ~~pharmaceutical formulation~~therapeutic composition, comprising:

~~(A)~~a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a monoclonal antibody or antigen binding fragment thereof, said monoclonal antibody being a human monoclonal antibody or a genetically--engineered monoclonal antibody, wherein~~:~~

(i) said antibody and said fragment recognize an epitope within residues 1-28 of beta-amyloid, and

(ii) said antibody and said fragment inhibit aggregation of beta-amyloid~~; and~~

~~(B) a pharmaceutically acceptable carrier.~~

175 (Amended). The ~~pharmaceutical formulation~~therapeutic composition of claim 174, wherein said ~~antibody is~~pharmaceutical formulation comprises a pharmaceutically acceptable carrier and a human monoclonal antibody.

176 (Amended). The ~~pharmaceutical formulation~~therapeutic composition of claim 174, wherein said ~~antibody is~~ pharmaceutical formulation comprises a pharmaceutically acceptable carrier and a genetically-engineered monoclonal antibody.

177 (Amended). The ~~pharmaceutical formulation~~therapeutic composition of claim 176, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

183 (Amended). A ~~pharmaceutical formulation~~therapeutic composition, comprising:

~~(A)~~a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a monoclonal antibody or antigen binding fragment thereof, said monoclonal antibody being a human monoclonal antibody or a genetically--engineered monoclonal antibody, wherein~~:~~

(i) said antibody is obtainable using residues 1-28 of beta-amyloid as an immunogen, and

(ii) said antibody and said fragment inhibit aggregation of beta-amyloid~~; and~~

~~(B) a pharmaceutically acceptable carrier~~.

184 (Amended). The ~~pharmaceutical formulation~~therapeutic composition of claim 183, wherein said ~~antibody is~~pharmaceutical formulation comprises a pharmaceutically acceptable carrier and a human monoclonal antibody.

185 (Amended). The ~~pharmaceutical formulation~~therapeutic composition of claim 183, wherein said ~~antibody is~~ pharmaceutical formulation comprises a pharmaceutically acceptable carrier and a genetically-engineered monoclonal antibody.

186 (Amended). The ~~pharmaceutical formulation~~therapeutic composition of claim 185, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

192 (Amended). A ~~pharmaceutical formulation~~therapeutic composition, comprising:

~~(A)~~ a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a monoclonal antibody or antigen binding fragment thereof, said monoclonal antibody being a human monoclonal antibody or a genetically-engineered monoclonal antibody, wherein~~:~~

(i) said antibody and said fragment recognize an epitope within residues 1-28 of beta-amyloid, and

(ii) said antibody and said fragment maintain the solubility of soluble beta-amyloid~~; and~~

~~(B) a pharmaceutically acceptable carrier~~.

193 (Amended). The ~~pharmaceutical formulation~~therapeutic composition of claim 192, wherein said ~~antibody is~~pharmaceutical formulation comprises a pharmaceutically acceptable carrier and a human monoclonal antibody.

194 (Amended). The ~~pharmaceutical formulation~~therapeutic composition of claim 192, wherein said ~~antibody is~~pharmaceutical formulation comprises a pharmaceutically acceptable carrier and a genetically-engineered monoclonal antibody.

195 (Amended). The ~~pharmaceutical formulation~~therapeutic composition of claim 194, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

201 (Amended). A ~~pharmaceutical formulation~~therapeutic composition, comprising:

~~(A)~~ a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a monoclonal antibody or antigen binding fragment thereof, said monoclonal antibody being a human monoclonal antibody or a genetically-~~-~~engineered monoclonal antibody, wherein~~:~~

(i) said antibody is obtainable using residues 1-28 of beta-amyloid as an immunogen, and

(ii) said antibody and said fragment maintain the solubility of soluble beta-amyloid~~; and~~

~~(B) a pharmaceutically acceptable carrier~~.

202 (Amended). The ~~pharmaceutical formulation~~therapeutic composition of claim 201, wherein said ~~antibody is~~pharmaceutical formulation comprises a pharmaceutically acceptable carrier and a human monoclonal antibody.

203 (Amended). The ~~pharmaceutical formulation~~therapeutic composition of claim 201, wherein said ~~antibody is~~pharmaceutical formulation comprises a pharmaceutically acceptable carrier and a genetically-engineered monoclonal antibody.

204 (Amended). The ~~pharmaceutical formulation~~therapeutic composition of claim 203, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

Applicant notes with appreciation the examiner's recognition that all of objections and rejections not reiterated in the official action of July 29, 2005, have been withdrawn by the examiner.

Claims 150, 151, 156, 157, 162, 163, 168 and 169 have been rejected under 35 U.S.C. §102(a) as being anticipated by Bickel.

All of the claims subject to this rejection have now been deleted, thus obviating this rejection.

Claims 150, 151, 156, 157, 162, 163, 168 and 169 have been rejected under 35 U.S.C. §102(b) as being anticipated by Stern.

All of the claims subject to this rejection have now been deleted, thus obviating this rejection.

The examiner has objected to claims 1-4 as the Markush group contains multiple elements that appear to be listed as one, wherein "genetically engineered antibody" and "antigen binding fragment" are recited. The examiner has required appropriate correction.

Claims 1-4 have now been deleted without prejudice toward the continuation of prosecution thereof in a continuing application. Accordingly, this objection has now been obviated.

Claims 150-173 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. This rejection is respectfully traversed.

Except for claims 155, 161, 167 and 173, all of claims 150-173 have now been deleted. Claims 155, 161, 167 and 173 have each been made dependent on claims which are not subject to this rejection. As the limitation "unit dose" no longer appears in any of the claims, this rejection has now been obviated. Reconsideration and withdrawal thereof are respectfully urged.

Claims 1-4 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. This rejection is respectfully traversed.

Claims 1-4 have now been deleting, thus obviating this rejection.

Claims 152, 158, 164, 170, 173-175, 178-180, 183, 184, 192, 193, 196-198, 201, 201, and 205-207 have been rejected under 35 U.S.C. §102(a) as being anticipated by Bickel. The examiner states that Bickel teaches a solution of human monoclonal antibody in standard ELISA buffer. The examiner states that the recitation in the claims of "pharmaceutical formulation" is interpreted as an intended use and is not given patentable weight in this art rejection. The examiner also states that the use of the antibodies of Bickel is not inconsistent with therapeutic utility. This rejection is respectfully traversed.

Respectfully, the examiner is incorrect that Bickel teaches a solution of human monoclonal antibodies in standard ELISA buffer. The only antibody disclosed by Bickel is AMY33. This antibody is first mentioned six lines from the bottom of the first paragraph on the second column of page 119 of Bickel, where it is cited with reference to publication 11 in the cited literature. Publication 11 is the Stern et al publication in Am J Pathol 134:973-978 (1989), which is of record in this case as reference GC. It can be seen from that document, and particularly the paragraph in the second column of 974, entitled "Generation and ELISA Screening of Antibodies," that the monoclonal antibodies described in that paper are "mouse MAbs," which are summarized in Table 1. Table 1, in the first column of page 974, includes the antibody AMY33. Thus, it is clear that AMY33 is a mouse antibody and not a human monoclonal antibody as stated by the

examiner. All of the present claims require that the antibody be a human monoclonal antibody or a genetically-engineered antibody or an antigen-binding fragment thereof. As AMY33 is neither a human monoclonal antibody nor a genetically-engineered monoclonal antibody nor a antigen-binding fragment of either, none of the present claims can be anticipated by Bickel. Bickel is thus similar to the Walker reference, which is also directed to a murine antibody. None of the present claims have been rejected over the Walker reference in the rejections discussed below. The present rejection should be inapplicable to the present claims for the same reason. Reconsideration and withdrawal of this rejection are respectfully urged.

Claims 150-152, 156-158, 162-164, 168-170, 173-175, 178-180, 183-184, 187-189, 192, 193, 196-198, 201, 201 and 205-207 have been rejected under 35 U.S.C. §102(b) as being anticipated by Gaskin as evidenced by Solomon. The examiner states that Gaskin teaches four human monoclonal antibodies that bind an epitope obtainable from residues 1-28 of human Aβ. The examiner states that a preamble is not a limitation when the claim is directed to a product and the preamble merely recites a property inherent in an old product defined by the remainder of the claim. The examiner states that the "pharmaceutical formulation" limitation is merely an intended use for an existing product. The examiner uses a 2002 reference of the present inventor to establish that antibodies raised against the first 28 amino acids of β-amyloid

inherently have anti-aggregating properties. Thus, the examiner considers this to be an inherent disclosure, and the antibodies of Gaskin must inherently have the required properties. The examiner states that the standard antibody solution for performing immunocytochemistry includes a solution of human monoclonal antibodies in standard ELISA buffer. This rejection is respectfully traversed.

The burden is on the examiner to establish that the antibodies of Gaskin necessarily either inhibit aggregation of human β-amyloid or maintain the solubility of soluble human β-amyloid. There is no suggestion in Solomon that the autoantibodies of Gaskin must necessarily and inherently have these properties. In establishing inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. See MPEP §2112.IV.

Accordingly, the examiner has not established that the autoantibodies of Gaskin must necessarily recognize an epitope within residues 1-28 of human β-amyloid or be obtainable using residues 1-28 of human β-amyloid and that such antibodies maintain the solubility of soluble β-amyloid or inhibit aggregation of human β-amyloid. In fact, the Gaskin publication itself would lead one to believe otherwise.

In the second paragraph of the discussion section on page 1184, Gaskin states:

> The nature of the reactive epitope was explored. The reactive epitope appears to reside in the region of amino acids 1-28 of the β-A_{1-40}. Further analysis suggests that the reactive epitope is conformational in that there is a significant contribution to the antigenic determinant by the region 29-40. In comparison with β-A_{1-40}, four- to eightfold greater concentrations of β-A_{1-28} were required in immunohistochemical studies to block the staining of amyloid plaque. It appears that the conformational nature of the reactive epitope is conserved in the amyloid plaques in situ. [Emphasis added]

The fact that the region 29-40 makes a significant contribution to the antigenic determinant would suggest that the epitope is not within residues 1-28 of human β-amyloid and certainly would suggest that it is not obtainable using residues 1-28 of human β-amyloid as an immunogen. Additionally, the fact that these antibodies were found in patients with Alzheimer's disease would suggest that these antibodies do not inhibit aggregation of human β-amyloid or maintain the solubility of soluble β-amyloid. If they did, then the patient should not have plaque. Thus, there is significant evidence that the antibodies of Gaskin do not anticipate any of the antibodies of the present invention.

Furthermore, Gaskin is directed to human monoclonal antibodies, but the reference suggests that these antibodies are pathogenic, not therapeutic. Note the last paragraph of Gaskin, where it states:

> However, these observations do not exclude the possibility that anti-β-amyloid antibodies may participate in complement

> fixation in vivo and contribute to the pathogenesis of AD.

Note also where it states, further in the paragraph:

> Therefore, a pathogenetic role of anti-β-amyloid antibodies cannot be dismissed at the present.

Accordingly, there would certainly be no motivation for anyone of ordinary skill in the art reading Gaskin to make a pharmaceutical formulation of those antibodies.

The examiner's point that "pharmaceutical formulation" was only in the preamble of the claim has been dealt with by amending the claims to insert this language into the body of the claims. Accordingly, this language cannot be ignored. A pharmaceutical formulation of an antibody and carrier requires that they be packaged in some way for use as a pharmaceutical. This is different from a mere pharmaceutical composition. A "formulation" requires that it be formulated in some way, as discussed in applicant's amendment of March 17, 2005. The term "unit dosage form" is no longer used in the claims in view of the new matter rejection. Nevertheless, a composition that is in the form of a pharmaceutical formulation must be physically different from a mere composition that is a combination of ingredients. Whether the form is in unit dosage form or otherwise, it still must be formulated, i.e., packaged as a pharmaceutical. The term "pharmaceutical formulation" as appearing in the body of the present claims is therefore a structural limitation and not merely a statement of intended use. By no stretch of the

imagination can the putatively pathogenic antibodies of Gaskin be considered to be a pharmaceutical formulation.

Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 150, 151, 156, 157, 162, 163, 168, 169, 178, 179, 178, 188, 196, 197, 205 and 206 have been rejected under 35 U.S.C. §102(a) as being anticipated by Walker as evidenced by Solomon. This rejection is respectfully traversed.

All of the claims subject to this rejection have now been deleted. All of the present claims are directed to human monoclonal antibodies or genetically-engineered monoclonal antibodies. Walker, like Bickel, only discloses mouse antibodies. Accordingly, this rejection has now been obviated. Reconsideration and withdrawal thereof are respectfully urged.

Claims 150-209 have been rejected under 35 U.S.C. §102(b) as being anticipated by or in the alternative 35 U.S.C. §103(a) as being obvious over Becker in view of Bickel or Gaskin. The examiner states that Becker teaches pharmaceutical formulations containing antibodies having specificity for β-amyloid peptide and that the peptides contain just the first 40 amino acids of the β-amyloid peptide. The examiner states that the reference teaches antibodies and fragments of antibodies, including chimeric, humanized, veneered, resurfaced or CDR-grafted antibodies, single-chain antibodies, as well as human monoclonal antibodies and genetically-engineered monoclonal antibodies.

The examiner states that the antibodies disclosed are presumed to recognize an epitope within 1-28 of β-amyloid or to be obtainable using residues 1-28 of β-amyloid as an immunogen. The examiner states that it would have been obvious to use the antibodies of Bickel and Gaskin to produce pharmaceutical formulations wherein the antibody is genetically engineered or a single-chain antibody as taught by Becker and well-established in the art. This rejection is respectfully traversed.

Becker does not expressly anticipate nor does it make obvious all of the elements of the claimed invention, and that which is disclosed is not enabled. There is nothing in Becker that clearly discloses to one of ordinary skill in the art that the antibody thereof recognizes an epitope within residues 1-28 of β-amyloid or is obtainable using residues 1-28 of β-amyloid as an immunogen. Becker requires a conformationally specific antibody. See column 5, lines 42-50 of Becker. There is nothing in Becker that would suggest that a conformationally specific epitope resides within residues 1-28 or could be obtainable using residues 1-28 of β-amyloid as an immunogen. There is no suggestion that residues 1-28 of β-amyloid alone will assume any particular conformation. More than a general description of the possible activity of conformationally specific antibodies is necessary in order to anticipate the present claims.

Furthermore, Becker nowhere states that the antibody thereof will inhibit aggregation of β-amyloid or will maintain

the solubility of soluble human β-amyloid. In fact, there is no indication why Becker considers that these antibodies might be therapeutically effective or what their mode of action might be. The burden is on the examiner to establish that every element of the claim is disclosed in Becker in order to support a 35 U.S.C. §102 anticipation rejection. The examiner has not done that. The examiner only states at page 17 of the Office action:

> The antibodies disclosed are presumed to recognize an epitope within residues 1-28 of beta amyloid or to be obtainable using residues 1-28 of beta amyloid as an immunogen.

However, the examiner has no explanation on what this presumption is based. An antibody raised against the first 40 amino acids of the β-amyloid peptide does not necessarily recognize an epitope within residues 1-28 of β-amyloid, and, even if it did, it would not necessarily inhibit aggregation of β-amyloid or maintain the solubility of soluble β-amyloid. The examiner concedes that Becker is silent on these properties.

The examiner does not explain how the conclusion is reached that the antibodies taught by Becker fall within the genus of antibodies as instantly claimed. The burden is on the examiner to establish that this is the case. If the examiner is stating that the antibodies of Becker will inherently have these properties, such a rejection is improper unless such inherency is certain. Reference is made to MPEP §2112.IV, under the heading "Examiner Must Provide Rational or

Evidence Tending to Show Inherency." This section states that the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. It cites a case to the effect that in establishing inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

Accordingly, the broad general disclosure of Becker, without any examples or rationale, cannot possibly serve to anticipate any of the present claims.

Furthermore, the Becker disclosure contains merely a suggestion of a direction of future research that might or might not lead to a therapeutic effect against Alzheimer's disease. It is effectively nothing more than a wish that such antibodies could be found. No antibody is made or tested in this disclosure, and there is not even a suggestion of what characteristics of antibodies might be expected to be operable. Indeed, at column 7, in the paragraph beginning at line 6, it states that some of the antibodies of Becker's "invention" demonstrate specificity for β-amyloid peptides that are predominantly β-sheet in conformation. In the paragraph beginning on column 7, line 33, it states that

another embodiment are antibodies that are specific for β-amyloid peptides that have adopted a random coil or alpha-helix conformation. Then, at column 7, in the paragraph beginning at line 39, the author merely states that the antibodies may be used in diagnostic, therapeutic or in diagnostic/therapeutic combinations. There is no suggestion that any one of the conformationally specific antibodies would be any better than any of the others, or that any of them would work at all or even why they might work. It is just a wish or a hope that some antibody that could be useful in therapeutics. This is hardly an enabling disclosure.

It is well established that a reference must contain an enabling disclosure in order to be available as a reference under 35 U.S.C. §102, *In re Hoeksema*, 399 F2d 269, 158 USPQ 596 (CCPA 1968). See MPEP §2121.01. It is true that MPEP §2121 states that when the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable, and the burden is on applicant to provide facts rebutting the presumption of operability. However, as discussed above, Becker does not expressly anticipate, nor does it make obvious all of the elements of the claimed invention. Furthermore, a mere review of the Becker specification, without any examples or even any theory of operability, would establish *prima facie* that it neither teaches how to make or how to use the antibodies wished for by Becker. Accordingly, Becker is not

available as a reference for either anticipation or obviousness.

With respect to obviousness, the disclosure of Becker does not provide motivation for one of ordinary skill in the art to use the antibodies of Bickel or Gaskin to produce pharmaceutical formulations. As discussed above, Bickel is not a human monoclonal antibody, and there is no suggestion that the antibody of Bickel is conformationally specific. There is nothing in Becker that would suggest in any way that the murine monoclonal antibody of Becker might be useful in the treatment of Alzheimer's disease and, therefore, Becker would provide no motivation to put the antibody of Bickel into a pharmaceutical formulation. No one of ordinary skill in the art reading Becker and Bickel would consider that the monoclonal antibody of Bickel would have the properties wished for by Becker for his conformationally specific antibodies.

Similarly, one of ordinary skill in the art would never consider combining Becker with Gaskin as the antibodies of Gaskin are considered to be pathogenic, not therapeutic. No one of ordinary skill in the art reading Gaskin would consider that any of those antibodies were the conformationally specific antibodies wished for by Becker that might have some kind of therapeutic activity against Alzheimer's disease even though Becker does not explain how it might be active as such a therapeutic. Accordingly, no combination of Becker with Gaskin could lead to the

pharmaceutical formulation of monoclonal antibodies of the present invention. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 1 and 3 have been rejected under 35 U.S.C. §102(b) as being anticipated by Solomon (1989). This rejection is respectfully traversed.

Claims 1 and 3 have now been deleted, thus obviating this rejection.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are, therefore, earnestly solicited.

Respectfully submitted,
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